DNA is the carrier of genetic information for almost every organism on Earth. Remarkably, the genetic alphabet is composed of only four nucleobases, which is a prominent example of the narrow selection of organic molecules forming the basis of life. Multiple selection pressures that operated during early chemical and biological evolution have been proposed as the driving force for the selection of the contemporary nucleobases. Above all, there must have been an extreme selection pressure for protection against intense ultraviolet radiation, and photostability was likely a decisive criterion giving some heterocycle analogues a selective advantage for their incorporation into the first informational polymers. Emphasis in this area by our research group has recently focused toward elucidating the structural and electronic elements that regulate DNA and RNA photostability from experimental and computational perspectives and applying this fundamental information to advance nucleic acid derivatives for photo-therapeutic and structural-biology applications. Understanding how functionalization regulates the electronic relaxation pathways in nucleic acid bases can assist in the development of therapeutic drugs, crosslinking agents, and fluorescent biomarkers. It may also hold the key for understanding the molecular origins of life. In this presentation, I will show that fundamental physicochemical investigations can be used to develop analogues of the canonical DNA and RNA nucleobases exhibiting more than 100 nm redshifted absorption spectra and nearly 100%...